Remarks

In the Office Action, the Examiner noted that claims 32-35 are allowed and claims 9-10, 16, 26, and 29-30 are objected to as being dependent upon a rejected base claim but would be allowable if rewritten in independent form including all the limitations of the base claim and any intervening claims. Claims 1, 5, 10, 14, 17-18, 21, and 29 are amended, and claims 8-9, 11-12, and 25-28 are canceled. The amendments are intended to put all the claims in condition for allowance and are not intended to concede to the correctness of the Examiner's position or to prejudice the prosecution of the claims prior to amendment, which claims are present in a continuation of the present application. Claims 1-5, 10, 13-24, and 29-35 are now pending in this application.

Amended claims 1, 17 and 18 are supported by originally-filed claims 1, 8-9 and 17-18.

Amended claim 5 is supported by originally-filed claims 5 and 8.

Amended claims 10 and 14 are supported by originally-filed claims 10 and 14, respectively.

Amended claim 21 is supported by originally-filed claims 21 and 25-26.

Amended claim 29 is supported by originally-filed claim 29.

The Brief Description of Figures 6A and 6B is amended to clarify the samples associated with certain data in those Figures. Those amendments are supported at page 41, lines 10-21 and page 46, lines 3-28 of the specification.

The Examiner rejected claims 1, 5, 8, 11-13, 15, 17-19, 21-22, 25, and 27-28 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent Publication No. 2002/0193326 (Sukhatme). The Examiner also rejected claims 1, 5, 8, 11-13, 15, 17-19, 21-22, 25, and 27-28 under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent Publication No. 2002/0193326 in view of Applicant's alleged admission on pages 2 and 26 of the specification. The Examiner further rejected claims 1-5, 8, 11-15, 18-22, 25, 27-28, and 31 under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent Publication No. 2002/0193326 in view of Arap et al. (Science, 279:377 (1996)) and Applicant's alleged admission on pages 2 and 26 of the specification. As these rejections may be maintained with respect to the pending claims, they are respectfully traversed.

Sukhatme is generally directed to methods of inhibiting proliferative diseases characterized by increased production of TGF-β and angiogenic activity (paragraph 0006, lines 1-5), i.e., TGF-β mediated angiogenic activity (paragraph 0006, lines 12-15). It is disclosed that TGF-β mediated angiogenesis can be inhibited with a molecule such as an anti-TGF-β antibody, a TGF-β antagonist, a soluble form of the TGF-β receptor, an antisense TGF-β oligonucleotide, or a molecule that blocks the interaction of TGF-β with receptors (paragraph 0008), as TGF-β1 directly inhibits the resolution phase of endothelial cell growth and migration (paragraph 0028, lines 5-9). It is also disclosed that such molecules can be used in combination with one or more additional antiangiogenic molecules, e.g., angiostatin, endostatin or restin, or fragments thereof (paragraphs 0009 and 0123). Endostatin is disclosed as an inhibitor of the initiation phase of angiogenesis which may be additive or synergistic with agents which inhibit TGF-β-mediated angiogenesis (paragraph 0123).

It is further disclosed that the invention includes fusion and chimeric proteins comprising an antiangiogenic protein, which may be prepared by recombinant means, that can be made up of a combination of two or more antiangiogenic proteins (e.g., angiostatin and endostatin) or an antiangiogenic protein in combination with a targeting agent (e.g., endostatin with epidermal growth factor or RGD peptides) (paragraph 0046, lines 11-21). Sustained release delivery systems are also disclosed (paragraph 0082).

Example 5 in Sukhatme shows that the administration anti-TGF-β antibodies to athymic mice implanted with RCC tumor cells resulted in a decrease in tumor size, possibly due to a decrease in the number of microvessels in the treated group.

Applicant's admissions at pages 2 and 26 of the specification are that kringle 5 of plasminogen, angiostatin (kringle 1-4 of plasminogen), tumstatin, canstatin, anti-thrombin fragment and retinal pigment derived factor, and alginate polymers, are known.

Arap et al. disclose that three peptides motifs, RGD, NGR and GSL, were identified by *in vivo* selection of phage peptide libraries for peptides that home to the vasculature (pages 377-8). RGD-4 (CDCRGDCFC) and CNGRC (a NGR peptide) were cyclized and then conjugated to doxorubicin, a drug with anti-angiogenic activity (page 378 and footnote 18). The conjugates or doxorubicin alone were administered to mice bearing tumors from MDA-MB-435 human breast carcinoma cells (page 374). The doxorubicin-RGD-4C conjugate treated mice outlived the

doxorubicin treated mice, had smaller tumors, less spreading to regionally lymph nodes, and fewer pulmonary metastasis (pages 378-9). It is disclosed that similar efficacy was observed with the CNGRC-doxorubicin conjugate (page 379). The authors note that the efficacy of the CNGRC conjugate may be derived entirely from vascular targeting because NGR peptides do not bind to MDA-MD-435 cells (page 380).

None of the cited documents, alone or in combination, disclose or suggest a chimeric polypeptide having an endostatin polypeptide with a targeting moiety at the C-terminus, wherein the amino acid at position 125 in the endostatin polypeptide is not proline, a host cell transformed with recombinant DNA encoding such a chimeric polypeptide, or methods of using a chimeric polypeptide which comprises an endostatin polypeptide with a targeting moiety at the C-terminus, e.g., a sustained release dosage form comprising alginate and the chimeric polypeptide.

Nor do the cited references provide a reasonable expectation that a C-terminally modified endostatin is necessarily more potent than wild-type endostatin.

Accordingly, withdrawal of the § 103(a) rejections is respectfully requested.

CONCLUSION

Applicant respectfully submits that the claims are in condition for allowance and notification to that effect is earnestly requested. The Examiner is invited to telephone Applicant's attorney (612) 373-6959 to facilitate prosecution of this application.

If necessary, please charge any additional fees or credit overpayment to Deposit Account No. 19-0743.

Respectfully submitted,

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Date March 16, 2004

By

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CERTIFICATE UNDER 37 CFR 1.8: The undersigned hereby certifies that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail, in an envelope addressed to: Mail Stop AF, Commissioner of Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on this 16th day of March, 2004.

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